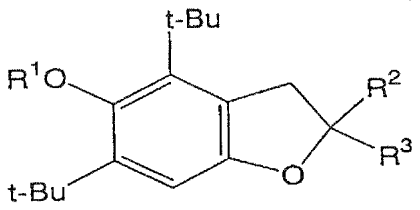
REMARKS

The Office Action of January 13, 2009, has been carefully studied. Claims 17-35 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

The Claimed Invention

Claims 17-35 are drawn to a method for treating fatty liver or hepatic disease by administering a compound of the formula (1):

[Chemical Formula 3]



(1)

where

R^1 is a hydrogen atom, an acyl group, or an arylalkoxycarbonyl group; and

R^2 and R^3 are each independently a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkenyl group, or a substituted or unsubstituted alkynyl group, or R^2 and R^3 may jointly form a cycloalkyl group,

to a patient in need of such treatment.

The specification defines "hepatic disease" at paragraph 0033 on page 13. In the present application "hepatic disease" refers to a disease that involves the leakage of hepatic enzymes, such as AST, by damage caused to cells constituting the liver. Enzyme leakage from the liver cells means that the liver cells are injured by various causes, such as accelerated hepatic metabolism and activation of Kupffer cells or hyperlipidemia, and infection, to leak intracellular enzymes into the blood. This hepatic enzyme leakage increase with the onset and progression of hepatic disease. The leakage suppressing action of the compounds of the present invention on hepatic enzymes is considered to be the outcome of suppression of damage to the liver cells.

Claims 17-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al., US 5,574,178 in view of Tsujii et al., US 5,043,354. The Examiner concedes that Tamura fails to teach that the compounds would be useful in treating fatty liver disease. The Examiner has cited Tsujii for teaching that benzofuran antioxidants can be used to treat "disorders of the liver." The Examiner alleges that the mitochondrial toxicity of amiodarone and the B0 and B2

analogues of amiodarone appears to be due to the coupling of the benzofuran ring to the p-hydroxy-benzene structure rather than simply to the benzofuran ring.

This rejection is respectfully traversed.

Attention is directed to Spaniol et al., *Journal of Hepatology* **35** 2001 628-636, previously submitted. Spaniol described on page 533, right column, lines 3-5, that the essential structure associated with mitochondrial toxicity appears to be the **benzofuran ring**. This article further describes on page 634, left column, lines 4-7 from the bottom, that since C1 and D2 caused no significant impairment of mitochondrial functions, the diethylaminoethoxy group and the benzene ring are not essential for the mitochondrial toxicity of amiodarone and analogues. The structures of amiodarone, B0, B2, C1 and D2 are shown in Spaniol.

These descriptions in Spaniol, particularly the latter description, would not lead one skilled in the art to expect that the mitochondrial toxicity of amiodarone would be due to the coupling of the benzofuran ring to the benzene ring. It is respectfully submitted that the Examiner's allegation that the coupling of the benzofuran ring to the p-hydroxy-benzene structure does not contribute to mitochondrial toxicity is not supported by the evidence shown in Spaniol.

The Examiner further alleges that, based upon the teachings of Masazumi et al., JP 05-320169, Royer et al., US 3,808,236, Ookasawa et al., JP 1-213276 and Cynshi et al., US 6,133,279, that the skilled artisan would reasonably believe that the benzofuran ring is not the cause of the mitochondrial toxicity of amiodarone and the B0 and B2 analogues of amiodanone, to support the above-mentioned allegation.

Regarding these four patents cited by the Examiner in support of the first allegation, the benzofuran rings of the benzofuran derivatives disclosed in these patents have unique functional groups, such as methylenedioxy plus carboxamide groups, nitro groups, aromatic groups, and hydroxy, as well as t-butyl groups, respectively, all of which may alter the properties of the benzofuran ring of amiodarone to remove the mitochondrial toxicity from the ring. Therefore, even if the benzofuran derivatives disclosed in the cited patents exhibited no mitochondrial toxicity of amiodarone, this fact would not lead one skilled in the art to believe that the benzofuran ring of amiodarone is not the cause of the mitochondrial toxicity of amiodarone. Thus, the patents do not support this first allegation.

Accordingly, one skilled in the art would not have expected from the disclosures of Tamura and Tsujii that the compound of claim 17 is useful for treating fatty liver or

hepatic disease, as defined in the present specification, before the priority date of the present application. Therefore, it is respectfully submitted that claims 17-34 are not obvious over Tamura in view of Tsujii.

The Examiner has rejected claim 34 as being obvious over Tamura in view of Tsujii. However, claim 34 is directed to a method for reducing the amount of aspartate aminotransferase leaking from liver cells into the blood. Neither Tamura nor Tsujii mentions leakage of aspartate aminotrasnferase from the liver cells into the blood. Because of this, one skilled in the art would never have been motivated to use the compounds in Tamura to reduce the leakage of aspartate aminotransferase from the liver cells into the blood before the priority date of the present application. Thus, particularly claim 34 and newly added claim 35 are not obvious over Tamura in view of Tsujii.

As noted above, the present specification at page 8, paragraph 0033, makes it clear that the compounds claimed herein reduce the amount of the enzyme, such as aspartate transferase, leaking from liver cells into the blood, and that these compounds also suppress hepatomegaly.

The Examiner has cited *KSR International Co. v. Teleflex, Inc.*, 550 US 2007, for the proposition that where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, one of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. However, Tamura discloses compounds that have anti-oxidative activity that are useful for treating ischemic diseases, such as arterial sclerosis and myocardial infarction. These diseases are not fatty liver or diseases caused by leakage of aspartate aminotransferase form the liver cells into the blood. Tsujii discloses compounds said to be useful in treating diseases caused by reactive oxygen species and organic radicals, including disorders of the liver. However, since these compounds are also anti-oxidants, there is no reason to believe that these compounds act in the same way as the compounds claimed herein.

The identifiable solutions in Tamura and Tsujii are compounds that are anti-oxidants. The methods claimed herein, on the other hand, inhibit leakage of liver enzymes into the blood. This has nothing to do with oxidative stress, and therefore one skilled in the art would not be motivated to choose from the Tamura or Tsujii compounds to treat conditions in which enzymes leak from the liver into the blood.

The specification is quite clear, beginning at paragraph 0002, that while oxidative stress is presumed to be involved in the onset or progression of various hepatic diseases, the effects of antioxidant vitamins and other compounds on hepatic diseases associated with nonalcoholic catty liver lave been investigated and no conclusions have been obtained. Therefore, one skilled in the art would not look to antioxidants to treat the liver disease fatty liver or other liver disease as defined and claimed herein. Thus, Tamura and Tsujii really **teach away** from the herein claimed method, as both of these patents disclose treating liver diseases with anti-oxidant compositions.

Claims 17-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cynshi et al., US 6,133,279 in view of Ookawa et al., JP 01213276. Cynshi is said to teach that the compounds having claimed formula (1) are antioxidants that can be used as a preservative for the liver. The Examiner acknowledges that Cynshi does not teach the use of the compounds for treating fatty liver or hepatic disease, including aspartate aminotransferase leaking from the liver cells into the blood. Ookawa is said to teach a benzofuran derivative of formula (1) for treating or prophylaxis of dysfunction of liver, including fatty liver.

This rejection is respectfully traversed. It should be noted that there are significant structural differences between the compounds of Cynshi and those of Oogawa. Specifically, the Cynshi compound has two t-butyl groups but no aromatic group no the benzofuran ring. In contrast thereto, the Ookawa compounds always have an aromatic group at the 3-position of the benzofuran ring, which is likely greatly to influence the pharmaceutical activity of the benzofuran ring. One skilled in the art, appreciating these great structural differences between the two types of compounds, would not apply the teachings of Ookawa to those of Cynshi.

It should be noted that neither Cynshi nor Ookawa discloses or suggests treating leakage of aspartate aminotransferase from the liver cells into the blood. In particular, claim 34 and new claim 35 are in no way suggested by the combination of Cynshi and Ookawa.

Moreover, one skilled in the art would not look to antioxidants as disclosed by Cynshi and Ookawa to treat fatty liver and liver diseases caused by aspartate aminotransferase or other liver enzymes from leaking from the liver cells into the blood.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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